

### REMARKS

Upon entry of the present amendment, claims 1-62 are pending in the above-referenced patent application and are currently under examination. Claims 11, 13-44, 49 and 54-62 have been withdrawn. Reconsideration of the application is respectfully requested.

Applicants thank the Examiner and the Primary Examiner for their time, comments and helpful discussion during the Interview on June 4, 2007. During the June 4 interview, the Trembl reference was discussed, and a consensus was reached that Trembl does not disclose compositions having saccharides in the range of between about 53% and about 75% w/w of the instant claims. Applicants also thank the Examiner for the Interview on June 5, 2007, discussing surprising results of the invention and entry of same.

The claims are rejected in various combinations under 35 U.S.C. § 103(a). Each of these rejections is addressed below in the order set forth by the Examiner.

#### **I. FIRST REJECTION UNDER 35 U.S.C. § 103(a) OVER PARK AND TREMBL**

Claims 1-8, 10, 12, 45-48, 50 and 52-53 have been rejected under 35 USC § 103(a) as allegedly being obvious over Park and Trembl. Applicants respectfully traverse the rejection in view of the comments below.

Although Applicants believe that no prima facie case of obviousness has been established, Applicants can rebut a prima facie case of obviousness by a showing of objective evidence demonstrating that the claimed subject matter is nonobvious.

MPEP § 716.02 provides:

Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (differences in sedative and anticholinergic effects between prior art and claimed antidepressants were not unexpected). In *In re Waymouth*, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974), the court held that unexpected results for a claimed range as compared with the range disclosed in the prior art had been shown by a demonstration of "a marked improvement, over the results achieved under other

ratios, as to be classified as a difference in kind, rather than one of degree." Compare *In re Wagner*, 371 F.2d 877, 884, 152 USPQ 552, 560 (CCPA 1967) (differences in properties cannot be disregarded on the ground they are differences in degree rather than in kind); *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) ("we generally consider a discussion of results in terms of 'differences in degree' as compared to 'differences in kind' . . . to have very little meaning in a relevant legal sense").

MPEP § 716.02(a) also provides that "[e]vidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)." Furthermore, the "[p]resence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)."

Applicants submit herewith a declaration by Dr. Martin Jones ("the Jones declaration"), which establishes unexpected and surprising properties for the lyophilized mannitol beads of the present invention.

**1. Spherical beads with a smooth morphology are unexpectedly prepared using mannitol of between about 53% and about 75% (w/w)**

Dr. Jones declares in paragraph 5 of the Jones declaration that the instantly claimed range of mannitol of between about 53% and about 75% (w/w) is a critical range for the lyophilized beads of the present invention. Within this range, the beads are reproducibly spherical with a smooth morphology (see pictures in paragraph 5 of the Jones declaration). Outside of this range, the beads can be non-spherical, and are characterized by a rough surface having pits and protrusions. The pictures in paragraph 5 of the Jones declaration show SEM images of mannitol beads at 60% and 65% (w/w) having spherical shapes and smooth morphology, while mannitol beads at 43% and 50% (w/w) are semi-spherical to spherical and characterized by protrusions, pits and craters on the bead surface.

**2. Mannitol beads unexpectedly afford spherical beads with a smooth morphology as compared to beads of other saccharides**

In paragraph 6 of the Jones declaration, Dr. Jones declares that the use of mannitol in the claimed range, rather than other saccharides or oligosaccharides, provides

lyophilized beads that are reproducibly spherical with a smooth morphology. The pictures in paragraph 6 of the Jones declaration show the effect on bead morphology of using trehalose versus using mannitol. The beads made using mannitol are smooth and spherical (E and F). In contrast, the beads made using trehalose (A and B) form a shiny, clear, irregular shaped mass that adheres to the bottom of the container, even where the % (w/v) of trehalose matches that of mannitol (A versus E). The beads made from trehalose did not lyophilize, and any resemblance to spherical shape by the trehalose beads prior to lyophilization was subsequently lost upon lyophilization.

**3. The present invention unexpectedly provides lyophilized mannitol beads that are substantially crystalline**

Dr. Jones declares in paragraph 7 of the Jones declaration that the lyophilized mannitol beads of the present invention, surprisingly, are substantially *crystalline* rather than glassy and amorphous. Dr. Jones further declares that lyophilized beads of the prior art are glassy and amorphous, and are thus unable to make the beads of the present invention that are reproducibly spherical with a smooth morphology. The powder x-ray diffractogram for the glassy, amorphous structure demonstrated an amorphous halo with no evidence of crystallinity. The powder x-ray diffractograms for the lyophilized beads of the invention were consistent with the  $\delta$ -polymorph of crystalline mannitol. Accordingly, the lyophilized mannitol beads of the present invention demonstrate a high degree of crystallinity.

**4. The use of mannitol in the claimed range unexpectedly provides lyophilized beads that are reproducibly the same size**

In paragraph 8 of the Jones declaration, Dr. Jones declares that the surprising nature of the lyophilized beads of the present invention is also exemplified by the reproducibility and homogeneity of the size of the lyophilized beads. Using three beads from each excipient formulation of Table 1 in the instant application, bead cross-section was measured. The bead diameter data demonstrate that the lyophilized mannitol beads of the present invention have a high degree of uniformity, as determined by the standard deviation (SD) and the coefficient of variation (%CV). The prior art trehalose beads have a %CV of around 6.5%, while the

lyophilized mannitol beads of the present invention have a %CV of from 0.70 to 2.44, significantly lower than that for the trehalose beads. The higher CV numbers for the trehalose beads indicate a larger degree of variability and less reproducibility in the diameter of the trehalose beads, as compared to the mannitol beads of the present invention. Accordingly, the lyophilized mannitol beads of the present invention are surprisingly uniform, as compared to beads with a similar % w/v trehalose.

In view of the Jones declaration providing unexpected and surprising results for the lyophilized mannitol beads of the present invention, Applicants respectfully submit that the claims of the instant invention are not obvious under 35 U.S.C. § 103(a) over Park and Trembl. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

## **II. SECOND REJECTION UNDER 35 U.S.C. § 103(a) OVER PARK, TREML AND KELLOGG**

Claims 8 and 50 have been rejected under 35 USC § 103(a) as allegedly being obvious over Park, Trembl and Kellogg. Applicants respectfully traverse the rejection in view of the comments below.

In view of the Jones declaration providing unexpected and surprising results for the lyophilized mannitol beads of the present invention, Applicants respectfully submit that the claims of the instant invention are not obvious under 35 U.S.C. § 103(a) over Park, Trembl and Kellogg. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

## **III. THIRD REJECTION UNDER 35 U.S.C. § 103(a) OVER PARK, TREML AND SHIVELY**

Claims 9 and 51 have been rejected under 35 USC § 103(a) as allegedly being obvious over Park, Trembl and Shively. Applicants respectfully traverse the rejection in view of the comments below.

In view of the Jones declaration providing unexpected and surprising results for the lyophilized mannitol beads of the present invention, Applicants respectfully submit that the

claims of the instant invention are not obvious under 35 U.S.C. § 103(a) over Park, Treml and Shively. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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